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A STUDY OF CEREBROSPINAL FLUID DYNAMICS

IN

IDIOPATHIC INTRACRANIAL HYPERTENSION

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CERTIFICATE

This is to certify that this dissertation titled **"A STUDY OF CEREBROSPINAL FLUID DYNAMICS IN IDIOPATHIC INTRACRANIAL HYPERTENSION"** submitted by **Dr. P.MAGESH** appearing for the M.Ch BRANCH II Neurosurgery – 5 year course, examination in August 2011, is a bona fide work done by him during the study period under my direct guidance and is being submitted to the Tamil Nadu Dr. M.G.R Medical University Chennai in partial fulfilment of the requirements of the course.

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DECLARATION

I, Dr. P.MAGESH, solemnly declare that this dissertation "**A STUDY OF CEREBROSPINAL FLUID DYNAMICS IN IDIOPATHIC INTRACRANIAL HYPERTENSION**" was done by me at the Institute of Neurology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai under the guidance and supervision of the Professor of Neurosurgery, Institute of Neurology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3, between 2008 and 2011.

This dissertation is submitted to the Tamil Nadu Dr.M.G.R. Medical University, Chennai – 32 in partial fulfilment of the University requirements for the award of the degree of M.Ch., Neurosurgery.

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CONTENTS

INTRODUCTION

Idiopathic intracranial hypertension (IIH) is the clinical syndrome of elevated intracranial pressure, without hydrocephalus or mass lesions and with normal cerebrospinal fluid (CSF) composition. The condition has been known to exist for over a hundred years and has been described by various names including the previously popular pseudo tumour cerebri and benign intracranial hypertension, the variation in nomenclature reflecting the continuing uncertainty about the precise nature of the condition as also the variations in the ideas of origin, diagnostic and treatment methods.

The precise underlying mechanism of increased CSF pressure and which intracranial compartment is primarily involved in the absence of ventricular dilatation resulting in IIH is still unclear. Several theories for IIH pathophysiology have been put forth based on neuroimaging and CSF hydrodynamic studies. These include obstruction or resistance to CSF outflow at the level of the arachnoid granulations, increased rate of CSF formation and alteration in the elasticity of the brain parenchyma and intracranial blood vessels, obstruction to venous outflow at the level of the superior sagittal sinus, and reduction in the capacity of the cranial and spinal subarachnoid space to expand.

There is ample evidence from infusion and perfusion studies that IIH is associated with an impairment of outflow of CSF, i.e. defective absorption, hence the role of CSF dynamics studies in diagnosis, and possibly in exercise of management options and follow up.

This study analyses the role of resistance to outflow of CSF (R_{out}) measurement obtained by CSF dynamics study in the diagnosis of IIH, employing the simple bedside saline manometry and improvised bolus injection method [The Madras Institute of Neurology (MIN) method].

AIM OF THE STUDY

- To measure the resistance to outflow of CSF (R_{out}) , the opening pressure (P_o) and the pressure-volume index (PVI) in patients with Idiopathic Intracranial Hypertension (IIH) by bolus lumbar injection method.

- To evaluate the usefulness of cerebrospinal fluid outflow resistance (R_{out}) measurement in the diagnosis of Idiopathic Intracranial Hypertension (IIH).

- To compare the value of cerebrospinal fluid outflow resistance (R_{out}) measurement with opening pressure (P_o) measurement in the diagnosis of Idiopathic Intracranial Hypertension(IIH).

REVIEW OF LITERATURE

Literature review is done under the following headings:

1. ***1.*** Historical background
2. ***2.*** Diagnostic criteria
3. ***3.*** CSF physiology
4. ***4.*** Pathogenesis and altered CSF dynamics
5. ***5.*** Methods to assess changes in CSF dynamics

1. HISTORICAL BACKGROUND

The German physician Heinrich Quincke (1893) published the first description of the condition, calling it 'meningitis serosa'[1]. This appeared to be preceded by case reports describing the same condition as early as 1866 by Bouchat (reported by Passot[2], 1913) who, introduced the 'pseudo' concept, speaking of 'pseudo-meningitis'. A second German neurologist, Max Nonne, (1904) identified cases of apparent cerebral tumour whose subsequent clinical course appeared to preclude a diagnosis of tumour, coining the term 'pseudotumour cerebri'[3] . From 1931 onwards, an English neurologist, Sir Charles Symonds, wrote a series of papers describing children who had elevated intracranial pressure in association with middle ear disease, which he called 'otitic hydrocephalus', suggesting that the raised pressure was a result of excess cerebrospinal fluid (CSF)[4,5,6].

By the turn of the 20th century, the terms serous meningitis and pseudotumour cerebri had been adopted, but diagnosis relied on clinical features or postmortem findings. Cerebral pneumography permitted further study of the condition in live patients and this was later to be enhanced by ventriculography and encephalography. Around this time Davidoff and Dyke (1956) published a report of 15 cases with normal cerebral pneumography, all of whom improved with cranial decompression[7].

In 1937, the American neurosurgeon Walter Dandy described 22 cases of 'intracranial pressure without brain tumour' and is credited with the first diagnostic criteria for the condition[8].

Foley (1955) published a detailed study dividing cases of the condition into those associated with ear disease and those with no known cause of raised intracranial pressure[9]. He regarded hydrocephalus as an inappropriate term, since the cerebral ventricles were not enlarged and introduced the name 'benign intracranial hypertension' for non-otitic cases. He described amongst this cohort of predominantly female, young, overweight patients "a variety of proposed aetiological agents so numerous and diverse that one must suspect that none is a direct cause." The term benign intracranial hypertension was used for many years until

several reports of severe visual loss in the condition rendered the term 'benign' inappropriate.

Corbett and Thompson(1989) suggested the term "Idiopathic Intracranial Hypertension" as the previous terms do not adequately describe the disorder and emphasize the severity of the condition, though it is to be noted that Buchheit et al had in 1969 itself proposed the term "Idiopathic Intracranial Hypertension"[10,11] .The late 1970s and early 1980s saw papers on mechanism by Johnston (1973, 1975), Fishman (1979, 1984), Rottenberg et al. (1980) and Donaldson (1981). The consensus favoured a primary disorder of CSF dynamics, with the creation of an imbalance between formation and absorption resulting in an increase in CSF volume. Reid et al. (1980, 1981) favoured brain oedema based on Computerized Tomogram(CT) evidence of ventricular size, Sugerman et al. (1995, 1999) implied causative role for obesity, and King et al. (1995) and Karahalios et al. (1996) suggested a much expanded causative role for increased cranial venous outflow pressure[12,13]. Idiopathic intracranial hypertension remains quite perplexing and fascinating, despite a century or more of investigation and study.

2. DIAGNOSTIC CRITERIA

Dandy criteria:

In his original paper, Dandy (1937) describes in detail the clinical features of the condition in 22 cases, but does not actually list the diagnostic criteria. The first specific listing of the 'modified Dandy criteria' was that by Smith in 1985, his list being as follows[14] :

1. Signs and symptoms of increased intracranial pressure (headaches, nausea, vomiting, transient obscurations of vision, papilloedema).
2. No localizing neurological signs otherwise, with the single exception being unilateral or bilateral abducens nerve paresis.
3. Cerebrospinal fluid which can show increased pressure but with no cytological or chemical abnormalities otherwise.
4. Normal to small symmetrical ventricles must be demonstrated (originally required ventriculography, but now demonstrated by computed tomography).

These 'modified' criteria have themselves been modified in subsequent papers.

Radhakrishnan et al. (1994) have listed the following criteria for the diagnosis of IIH[15] :

1. Signs and symptoms of increased intracranial pressure.

2. No localizing neurological signs, in an awake and alert patient, other than abducens nerve paresis.
3. Normal neuroimaging except for small ventricles or an empty sella.
4. Documented increased pressure (250mm of water or more) but a normal composition of the cerebrospinal fluid.
5. Primary structural or systemic causes of elevated intracranial venous sinus pressure excluded (for example, sinovenous thrombosis, hyperviscosity syndromes, and right heart failure).

Other studies on this issue include those of Ahlskog and O'Neill (1982), Corbett(1983) and Carlow et al. (1987).

In their recent review, Sussman et al. (1998) added a sixth criterion : "benign clinical course apart from visual deterioration" [16].

Friedman and Jacobson in 2002 updated diagnostic criteria for IIH for purposes of routine patient management and for clinical trials and the following is their "Criteria for diagnosing idiopathic intracranial hypertension" [17].

1. If symptoms present, they may only reflect those of generalized intracranial hypertension or papilledema.

2. If signs present, they may only reflect those of generalized intracranial hypertension or papilledema.
3. Documented elevated intracranial pressure measured in the lateral decubitus position.
4. Normal CSF composition.
5. No evidence of hydrocephalus, mass, structural, or vascular lesion on magnetic resonance imaging (MRI) or contrast-enhanced CT for typical patients and MRI and MR venography for all others.
6. No other cause of intracranial hypertension identified.

A complete list, covering all the criteria included in the different studies, might read as follows:

1. Signs and symptoms of raised intracranial pressure.
2. Absence of focal neurological signs.
3. Measured increase in CSF pressure.
4. CSF of normal composition.
5. Normal imaging studies (including MRI / MRV) apart from possibly small ventricles and an empty sella.
6. Not attributable to another cause.
7. Benign clinical course apart from possible adverse effects of raised CSF pressure on the optic nerves.

This last is a slightly expanded version of the recent list offered by Friedman and Jacobson (2004).

The criteria as currently formulated in the International Headache Society's (IHS) classification of headache disorders (2nd edition) are outlined below[18]:

1. Alert patient with neurological examination that either is normal or demonstrates any of the following abnormalities:
    a. Papilloedema
    b. Enlarged blind spot
    c. Visual field defect
    d. Sixth nerve palsy
2. Increased CSF pressure (>200 mmH2O in the non-obese, >250 mmH2O in the obese) measured by lumbar puncture in the recumbent position or by epidural or intraventricular pressure monitoring.
3. Normal CSF chemistry (low CSF protein is acceptable) and cellularity.
4. Intracranial disease (including venous sinus thrombosis) ruled out by appropriate investigation.
5. No metabolic, toxic or hormonal cause of intracranial hypertension.

A presenting headache is attributed to idiopathic intracranial hypertension when the headache develops in close temporal relation to the increased intracranial pressure and improves after withdrawal of CSF. The headache should be progressive with at least one of the following:

a) Daily occurrence

b) Diffuse and/or constant non-pulsating pain

c) Aggravated by coughing or straining

3. CSF PHYSIOLOGY

CSF is physiologically produced by active secretion from cerebral arterial blood. The major site of this process is the choroid plexuses of the ventricular system, but the extrachoroidal production of CSF is responsible for a significant amount of the total CSF formation.CSF production rate can be assessed by means of continuous CSF drainage techniques or perfusing the subarachnoid spaces with a tracer and subsequently measuring its dilution[19].Unfortunately, both techniques have the limitation of averaging all possible dynamic components of CSF production. Therefore, although the normal average rate of CSF production in human beings is accepted to be 0.35 ml /min, very little is known about dynamic changes in its production rate and their clinical significance. CSF secretion is supposed to be proportional to brain

metabolism and tends to decrease with age.CSF flows from the lateral and third ventricles through the aqueduct of Sylvius to reach the fourth ventricle. Passage through the narrow aqueduct is pulsatile, and its flow velocity can be detected by phase-contrast MRI techniques. The study of the characteristics of CSF pulsations is promising and several MRI techniques have gained increasing interest for the modelling and the diagnosis of CSF dynamics disturbances.

Normally, CSF exits the fourth ventricle through the foramina of Magendie and Luschka, flows freely through the basal cisterns upwards towards the superior sagittal sinus and downwards towards the lumbar subarachnoid space. The spinal subarachnoid space accounts for a significant part of the compensatory reserve of the system, with a compliant venous network that can accommodate acute changes in intracranial volumes displacing CSF caudally. This volume-buffering mechanism is based on the free circulation of CSF fluid cancelling out all intracranial pressure (ICP) gradients and therefore protecting the brain from the risk of herniation. If the normal pathways of CSF circulation are viable such as in the case of communicating forms of hydrocephalus patients can tolerate acute rises in ICP up to 60mmHg without any subsequent adverse effect.

Re-absorption of CSF fluid into the venous compartment takes place predominantly through the arachnoid granulations of the sagittal sinus. The resistance to CSF outflow has been assessed in normal subjects as ranging from 6 to 10mmHg/ml/ min[20].In cases of disturbed CSF re-absorption through the physiological pathways, a secondary component of CSF re-absorption is the leakage directly into the brain parenchyma. This phenomenon can sometimes be visualized as a periventricular hypo-density along the horns of the lateral ventricles[21].

4. PATHOGENESIS AND ALTERED CSF DYNAMICS:

The pathogenesis of raised ICP in IIH remains unclear. IIH has become a 'disease of Theories' because of the many postulated hypotheses that have been put forward to explain its pathogenesis. No single theory has been able to provide a comprehensive answer and so there remains little consensus as to its cause. According to the Monro-Kellie rule, anything added to the blood, CSF, or brain volume or anything impeding CSF or venous egress would be expected to increase ICP.

The causes which could increase the intracranial pressure are as follows:

Increased cerebral volume	increased interstitial fluid (ISF) volume
	increased blood volume
	increased tissue volume
Increased CSF production rate	
Increased CSF outflow resistance	
Increased cerebral arterial pressure transmitted to capillaries (loss of auto regulation)	
Increased cerebral venous pressure	leading to increased venous blood volume and increased ISF volume
	leading to reduced CSF outflow

CT Scan offered a way of assessing cerebral volume in IIH, albeit somewhat crudely. A reduction in the size of the ventricular system, indicating an increase in cerebral volume, was reported in some studies[22,23.24], but not in others[25], and it remains controversial as to whether cerebral volume is significantly increased in IIH. The disagreement perhaps reflects heterogeneity of pathogenesis. The hope

has been expressed that MRI will provide a great deal more information about what is going on in IIH, but thus far there has not been an abundance of reported studies of cerebral and CSF volumes in IIH, nor of the composition of cerebral tissue. Moser et al[26] reported an increase in white matter water signal, suggesting diffuse mild oedema, and Gideon et al[27] detected increased water mobility in subcortical white matter.

Both studies required the use of special MRI sequences, routine sequences showing no abnormality. The brain in IIH has also been studied by positron emission tomography. Notably, no change in regional cerebral blood volume was found[28]. The most invasive studies of cerebral tissue in IIH were cerebral biopsies, which were reported by Sahs and Joynt to show evidence of interstitial cerebral oedema, but necropsies have not confirmed those findings, nor did a review of some of the original biopsy material of Sahs and Joynt[29,30].

Increased CSF production

Increased CSF production rate has been proposed as a mechanism of IIH. The production rate of CSF can be measured in patients, but the procedures (infusion or perfusion techniques) are invasive. In one study increased CSF production rate was reported in IIH[31]. However, most

investigators have not found CSF hyper secretion in IIH. An attempt at measuring CSF production rate noninvasively by recording CSF flow through the cerebral aqueduct using MRI did not support the view that CSF hyper secretion is important in IIH[32].

The only condition in which the CSF production rate is known definitely to be increased is choroid plexus papilloma, a fairly rare paediatric tumour. An IIH-like syndrome has not been reported in choroid plexus papilloma. Idiopathic intracranial hypertension would require a generalised increase in intracranial pressure without a significant pressure gradient across the cortical mantle, and without any capacity for the brain to be compressed. Mathematical modelling of ventricular size in the circumstance of increased CSF production predicts hydrocephalus, not IIH[33]. Experimental infusion of artificial CSF into the lateral ventricles of dogs leads to modest ventricular enlargement, not an IIH- like syndrome[34].

CSF outflow obstruction

Much more important and relevant is the likelihood that impaired outflow of CSF into the venous system is a cause of IIH. An increase in CSF pressure, either due to CSF overproduction or due to impaired absorption,

would be expected to lead to an increase in CSF volume, if the CSF space had the capacity for any expansion. Within a non-expansile skull and relatively non-expansile spinal canal, CSF could only easily accumulate at the expense of cerebral blood volume. In IIH there is neither a reduction in cerebral blood volume, nor an increase in CSF volume. If the proposition is that the impairment of outflow of CSF is a lesion at the arachnoid villi and granulations level, then there is no reason to expect any trans mantle pressure gradient, and it is easier to envisage this as a mechanism for IIH than Normal Pressure Hydrocephalus. Infants might represent a special case, as a non-acute increase in intracranial pressure may be expected to cause expansion of the skull vault, allowing the accumulation of CSF, either inside the ventricles or outside (external hydrocephalus). However, in the mathematical model of Rekate et al, an increase in CSF outflow resistance alone leads to hydrocephalus, and to generate the conditions found in IIH a reduction in brain compressibility is required as well[33].

There is ample evidence from infusion and perfusion studies that IIH is associated with an impairment of outflow of CSF. There is no direct evidence of dysfunction of arachnoid villi and granulations in IIH.

Abnormalities of arachnoid villi have, however, been noted in certain conditions which involve raised intracranial pressure.

Microscopy after subarachnoid haemorrhage has disclosed apparent obstruction of villi by cells and morphological changes in arachnoid villi and granulations[35].

The outflow resistance of CSF is known to be increased in experimental subarachnoid haemorrhage[36]. But the disturbance of CSF dynamics associated with subarachnoid haemorrhage is hydrocephalus, and the relevant site of CSF flow disturbance might be proximal to arachnoid villi and granulations.

Intracranial venous hypertension

The final mechanism for IIH is the obvious one of an increase in venous sinus pressure - obvious because lesions which increase venous sinus pressure (for example, dural arteriovenous malformations) or impede venous drainage (for example, venous sinus thrombosis, malignant obstruction of venous sinuses or jugular veins) are known to give rise to the same syndrome as IIH. Clearly superior sagittal sinus thrombosis will affect cerebral venous pressure and drainage and will also directly affect

CSF absorption, but any disorder causing a rise in venous pressure will secondarily have an effect on CSF absorption.

In the CT era it is in fact quite likely that cases of cerebral venous sinus thrombosis were misdiagnosed as having IIH, as the diagnosis was often made on the basis of the clinical picture, an unremarkable scan and a lumbar puncture.

Magnetic resonance imaging and magnetic resonance venography have improved the reliability of non-invasive detection of cerebral venous sinus thrombosis, but still some cases may be missed without catheter angiography or venography[37]. Recent reports of potentially prothrombotic abnormalities of coagulation in IIH may be construed as indicating that undetected cerebral venous sinus thrombosis remains a mechanism of IIH, although other interpretations are possible[38].

Some authors have suggested impaired CSF absorption due to resistance generated by raised venous pressure from venous outflow obstruction as a possible explanation . There is also considerable evidence that the majority of patients with IIH carry a stenosis in the transverse sinuses(TS), although there is debate on whether such a stenosis is a

cause or effect of the condition as some authors suggest such narrowing to be secondary to the raised ICP. Higgins et al. investigated 20 patients with IIH and 40 controls with MRV. They identified bilateral TS flow defects in 13 of 20 patients with IIH and in none of the 40 controls [39]. In a study by Bono et al., 14 patients with IIH who had bilateral TS stenoses were followed over a period of 6 years[40]. All patients had repeated MRV followed by lumbar punctures. Although, CSF pressure normalized in nine of the 14 patients during the follow-up period with medical treatment, TS stenosis persisted in all patients suggesting that TS defects may not be secondary to raised CSF pressure.

King et al reported briefly on a larger patient series. Fifteen out of 17 patients with IIH had raised superior sagittal sinus and proximal transverse sinus pressures with a drop in pressure in the distal transverse sinus. In four of these patients CSF was removed at the time of manometry with a resultant lowering of intracranial pressure, and that led to abolition of the apparent functional obstruction of the distal transverse sinus, which suggested to the authors that intracranial hypertension caused compression of the transverse sinus in some patients[41].

This study highlights the possibility that increases in CSF pressure and venous pressure can interact so that each makes the other worse. The authors imply that they do not consider the increase in venous sinus pressure to be the primary event in most of their patients. By contrast, Karahalios et al speculated that "most if not all aetiologies (of IIH) result in an increase in intracranial venous pressure as a final common pathway." In their series, venous outflow obstruction was detected by venography in five out of 10 patients studied. In the remaining five there was no obstruction but venous pressures were nevertheless increased, as were right atrial pressures with transmission of the raised central venous pressures back to the intracranial venous system. Karahalios et al discuss ways in which obesity might lead to raised central venous pressures, but conclude that the mechanism of increased central venous pressure in IIH remains obscure[42].

Obesity and IIH

The relation between IIH and obesity has long been recognised. Pressure in the CSF is higher in obese but otherwise normal compared to people of normal weight. An association between recent weight gain and the development of IIH has been established. Weight reduction and bariatric

surgery has long been part of the treatment strategy. There is some evidence that weight reduction is therapeutic[43].

The concept of Secondary IIH

Although considered to be idiopathic, detailed investigation may reveal venous outflow abnormalities in IIH patients. This had led to a distinction in terminology with "secondary IIH" commonly being attributed to conditions causing increased dural sinus pressures. Guiseffi et al proposed a criteria for assessing disease association in IIH, considering the need to identify the many conditions associated with it[44].

Criteria for assessing Secondary IIH[45]	
A	Meets Dandy's criteria
B	The condition should be proven to increase ICP
C	Treatment of the condition should improve the IIH
D	Properly controlled studies should show an association between the condition and IIH

The Digre's scale attempts to rank the probable association between various conditions and IIH based on the above[46] :

DIGRE' SCALE		
Proven association	meets 4 criteria	Obesity
Likely association	meets 3 criteria	Drugs: Kerprone, lindane
		Hypervitaminosis A
Probable association	meets 2 criteria	Steroid withdrawal
		Thyroid replacement in Children
		Hypoparathyroidism
		Addison's disease
		Uremia
		Iron deficiency anaemia
		Drugs: tetracyclines, nalidixic acid,danazol, lithium, phenytoin, amiodarone, Nitrofurantoin, ciprofloxacin, nitroglycerin.
Possible association	meets 1 criterion	Menstrual irregularity, OCP use, Cushing syndrome,Vitamin A deficiency, Minor head trauma, Behcet syndrome.
Unlikely association	meets no criteria	Hyperthyroidism,steroid use, Immunisation.
Unsupported association		Pregnancy, menarche.

Additional conditions that are not included in Digre's list but meet minimal criteria include:

1) Other drugs : isoretinoin, trimethprim-sulphamethoxazole, cimetidine and tamoxifen.

2) Systemic lupus erythematosus.

These are all considered treatable causal factors for IIH.

5. METHODS TO ASSESS CSF DYNAMICS; R_{out} MEASUREMENT:

The balance between CSF formation and absorption in holding the Intra Cranial Pressure(ICP) constant is given by the Davson equation[47]

$$ICP = F_r . R_{out} + P_{ss} = Er.R_{out} + P_{ss}$$

Where, F_r is CSF formation rate ; R_{out} is the resistance to CSF outflow ;

P_{ss} is the pressure in the sagittal sinus ; E_r is the CSF elimination rate.

Based on an average volume of 150ml, the turnover of CSF is 14% per hour.

Borgesen and Gjerris (1987) , based on study on 333 patients, related the formation rate and ICP as follows:

$$ICP = 3.0 + 0.3.R_{out}$$

They indicate that the normal production rate of CSF is 0.3ml/min[48].ICP is normally maintained by the resistance factor of CSF outflow, as given

by the Davson equation above. Regulation of CSF volume by means of outflow resistant factors, especially the venous part, is probably the major mechanism of protection of brain against lethal increases of ICP.

Human beings have the highest overall rate of CSF formation, the greatest efflux capacity and the lowest outflow resistance. A CSF outflow can sustain efflux rates of atleast 2.0ml/min[21].

Marmarou et al.(1978) introduced the PVI (Pressure Volume Index) reflecting the correlation between an increasing volume and the resulting pressure.

They measured the response of CSF pressure to a bolus injection and showed how to calculate both compliance and resistance to CSF flow. The PVI is given by the slope of the volume - log pressure curve. R_{out} measured by this method is given by the formula :

$$R_{out} = \frac{t2 \,.P0}{PVI \,.log\, P2/Pp.(Pp-P0)/(P2-P0)}$$

Where - P_0 is opening pressure

- P_p is the peak pressure

- P_2 is the instantaneous pressure at time t_2 on the recovery slope

- t_2 is the elapsed time from the instant of injection to the point at which P_2 is determined

Measurement of Resistance to CSF outflow (R_{out}) :

The aim is to measure the outflow rate of CSF from the CSF compartment.

The three methods in clinical practice are

1) Infusion tests

2) Bolus injections, and

3) Isotope dilution methods.

1) INFUSION TESTS :

These methods monitor ICP during infusion of synthetic CSF or Ringer's lactate. They are based on principle of injecting, infusing or perfusing artificial CSF intrathecally at either a constant rate or constant pressure and plotting the flow (ml/min) against ICP levels. The slope of the regression curve is an expression of conductance to CSF outflow (C_{out}) , and the reciprocal value is resistance to outflow ($R_{out} = 1/C_{out}$).

The calculation of R_{out} implies a constant rate of CSF production, and constant CSF and blood volumes, irrespective of the increases in ICP during the study. All methods give a possibility of CSF leak, which will result in too low R_{out} values. Three techniques have been described on this principle:

1. constant pressure servo controlled infusion method :– though more accurate, is time consuming and difficult.
2. constant infusion method: (Katzman test[51]): -- easy and not very time consuming, but the interpretation of plateauing of the induced pressure rises is difficult. Czosnyka et al. devised the computerised infusion test for measuring the R_{out} and other CSF parameters, and is simple, quick and less invasive[52].
3. constant infusion and constant pressure method: (lumbo ventricular perfusion method) –gives reliable results, but there is risk of infection.

2) BOLUS INJECTION TESTS :

The bolus technique is fast and simple, but is based on complex mathematical calculations. It is based on the first mathematical model of CSF pressure-volume which provides much of the basis for understanding the CSF dynamics, devised by Marmarou and verified

experimentally in his work. Using this model, the author described the pressure-volume index (PVI) as the volume required to increase ICP tenfold, in other words, as the compliance or the ability of the craniospinal system to accommodate the change in volume per unit change in pressure (dV/dP) over the whole physiological range of ICP.

Marmarou's model also allowed the identification of CSF outflow resistance (R_{out}) which is considered to be the impedance of flow offered by the CSF absorption pathways. Absorption of CSF fluid into the venous compartment takes place predominantly (in humans) through arachnoid granulations adjacent to the walls of the sagittal sinus. The nature of the CSF absorption is proportional to the pressure gradient between the CSF side of the granulation and the sagittal sinus .

The bolus CSF infusion method used in our clinical study involves injecting a known volume, usually 5 ml, into the lumbar subarachnoid space at a rate of 1 ml/s. Recording the baseline pressure just before injection (P_0), the maximum pressure immediately after injection (P_p), and the pressure after a time (t) from the injection (P_t) determines the R_{out} which is calculated from the following equation : $R_{out} = P_0/PVI \times \log$

$[(P_t/P_p) \times (P_p - P_0)/(P_t - P_0)]$ and the PVI which is also calculated using the equation: $PVI = dv/\log (P_0/P_p)$.

The bolus method seems more valuable in patients with increased ICP (high elastance/low compliance), that is, in patients with diffuse head injury and patients with idiopathic intracranial hypertension.

3) RADIO ISOTOPE DILUTION METHODS:

Radioisotope introduced intrathecally may depict production, transport and resorption of CSF. The tracer is followed by a gamma camera both in space and time over 1,6,24 hours. The pattern of distribution of CSF flow as illustrated by radioactive tracer, is not only an expression of the degree of obstruction to CSF outflow but also CSF volume.

CSF DYNAMICS STUDIES IN NORMAL SUBJECTS:

In a study of healthy volunteers using lumbar infusion method, Borgeson and Gjerris(1982) found a mean ICP of 11.1 mmHg and R_{out} of 9.1mmHg/ml/min[53].

Normal values of R_{out} in different studies are as under (mmHg/ml/min)

Ekstedt(1978)[50]	< 8.33
Sklar et al.(1979)[54]	< 10.00
Albeck et al(1991)[55]	< 9.1
Ramesh et al.(2005)[56]	< 9.6

The value of R_{out} increases with age[57]. Many studies have over a period of time proved the reproducibility and reliability of repeated R_{out} measurements employing more than one method described above.

R_{out} measurements in individuals with pseudotumour cerebri, the older term for IIH have shown elevated values in most patients. Many patients have been found to have normal or only slightly elevated ICP, especially in the later phase of the disease process.The studies by Gjerris, Calabrese and Janny have observed raised R_{out} in patients with IIH[62].

MATERIALS AND METHODS

The study was undertaken at The Institute of Neurology, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai, between April 2008 and February 2011.

The study was conducted on patients admitted in the Neurosurgical wards with a clinical diagnosis of Idiopathic Intracranial Hypertension, as suggested by the 'Modified Dandy criteria' .

All patients had headache of varying severity, persistent and constant for few weeks prior to admission, necessitating medical advice. The temporal profile of headache was suggestive of raised intracranial pressure in all of them. All patients had papilloedema clinically ,and were confirmed by the Neuro ophthalmologist of the Institute, and visual field charting were done. None had any focal neurological deficit after a thorough neurological examination, other than the lateral rectus palsy in a few. None had history of chronic medications. All patients had contrast enhanced CT and MRI Brain and MRV done to rule out venous sinus thrombosis and there was no evidence of hydrocephalus, mass or structural, or vascular lesions in any of them. All patients were alert and co-operative.

The approval of The Institutional Ethics Committee was obtained. All patients were explained in detail about the procedure and written informed consent was obtained. The CSF dynamics study was undertaken in all of them as per the method described below.CSF samples were sent for analysis and were found to be of normal composition in all.

The method of CSF dynamics study :

The bolus lumbar injection method advocated by Marmarou and improvised at the Institute of Neurology (MIN method) was used[56].

The apparatus consists of a saline stand, a one meter scale, an intravenous set, a three way adaptor, 20 G disposable lumbar puncture needle, syringes and 2% lignocaine for local anaesthesia.

The scale is mounted on the saline stand and the saline filled intravenous set is mounted and fixed over the scale as a manometer to allow readings to be taken directly. The saline column of the manometer is kept at 11cm H_2O, with the zero level adjusted to correspond to the spine of the patient, the level of the spinal needle. The saline filling up to 11cm, representing the normal intracranial pressure, is done to avoid the loss in pressure head by the volume of CSF that goes to fill the manometer. After explaining

the procedure and after obtaining informed written consent, the patient is positioned in the Right lateral decubitus position and under sterile aseptic precautions, lumbar puncture is performed with 20 G spinal needle and the needle is connected to the saline manometer through the 3-way adaptor without letting out any CSF. The patient is allowed to relax, extend lower limbs and neck, lying comfortably in Right lateral position, and the opening pressure, P_0 is noted after the saline column stabilises.

A known volume of saline, rV , usually 5ml is injected into the subarachnoid space at the rate of 1ml/second, through the 3-way port. The peak pressure, P_p , reached after the bolus injection is noted. The saline column falls gradually after reaching the peak. After a certain time, t (in minutes), the pressure recording in the manometer , P_t , is noted.

The CSF outflow resistance is calculated by the two step Marmarou's formula :

Step 1 :

Calculation of the pressure - volume index (PVI)

$PVI = rV/\log (P_p / P_o)$

Step 2 :

Calculation of resistance to outflow of CSF (R_{out})

$$R_{out} = \frac{t.P0}{PVI.\log Pt/Pp.(Pp-P0)/(Pt-P0)}\ cmH_2O/ml/min.$$

This value is divided by 1.36 to express in mmHg/ml/min. About 25 to 30 ml of therapeutic drainage of CSF was done in each case. The procedure was uneventful in all cases, and the patients tolerated well.

The details of the patient and the observations were recorded in a detailed proforma (vide Appendix 3).

The $P_{0,}$ PVI and R_{out} were recorded. The value of P_0 and R_{out} in establishing the diagnosis of IIH was studied.

The statistical analysis was done using the software SPSS version 11.5.

Figure – 1 : Materials

Figure – 2 : The Lumbar puncture

Figure - 3 : The Bolus injection

Figure - 4: The Saline Manometer

RESULTS

Forty seven patients with features of IIH treated during the period between April 2008 and February 2011were included in the study.

The details of the patients are shown in the table:

S. NO.	AGE	SEX	Opening Pres.	R out
1	33	F	31	11.4
2	28	F	21	9.4
3	40	F	18	6.9
4	45	M	37.5	16.9
5	27	F	37	5.8
6	32	F	15	2.8
7	37	F	19	22.6
8	29	F	42	53.4
9	40	F	40	4.3
10	36	M	16	43.7
11	21	F	45	8.1
12	28	M	33	4.7
13	26	F	25	10.3
14	36	F	35	6.6
15	45	M	14	27.1
16	30	F	25	27.8
17	28	M	49	15.1
18	49	M	21	10.9
19	24	M	65	17
20	48	F	38	48.5
21	27	F	42.5	21.4
22	30	F	27	28.5
23	15	F	19.5	14.3
24	19	F	83	38
25	33	F	41	4.1
26	42	F	47	61.2
27	24	F	39	5.1
28	40	F	60	18.3
29	23	M	33	6.9
30	22	F	64	25.1
31	40	F	55	10.1
32	27	F	25	7.3
33	37	F	24	13
34	40	M	26	10.9
35	30	F	23	7.8
36	32	M	19	3.2
37	41	F	60	17.9
38	29	F	41	7.9
39	40	M	38	16.2
40	18	F	26	8.3
41	27	F	35	11.5
42	24	M	40	13.5
43	15	F	21	9.1
44	26	F	35	6.2
45	42	F	18	12.2
46	22	F	26.5	14.9
47	30	F	18	8.9

Table – 1: Opening pressure and R_{out} values.

There were 34 females and 13 males, in the age group of 15 to 49 years.

Age distribution :

Age	No
<20	4
20-30	22
30-40	14
40-50	7
Total	47

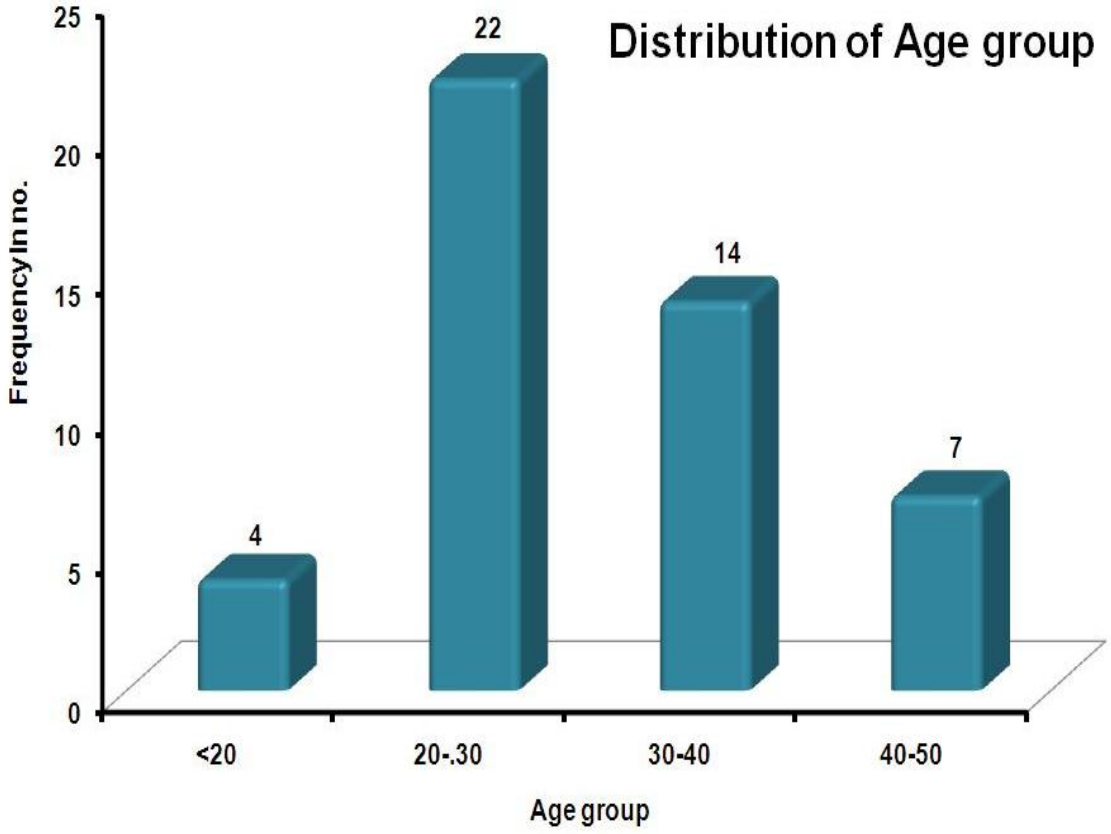

Figure – 5 : Age Distribution

Sex distribution :

Gender	No
Male	12
Female	35
Total	47

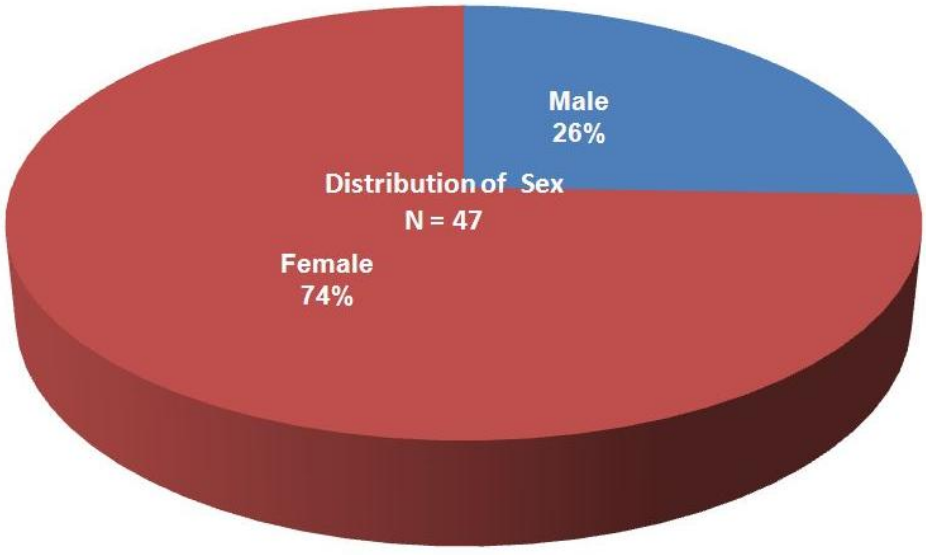

Figure – 6 : Sex Distribution

The opening pressure ranged from 14 to 83 cmH_2O.

The resistance to CSF outflow ranged from 2.8 to 61.2 mmHg/ml/min.

Of the 47 patients, 31 had raised resistance to CSF outflow. The rest of the patients had R_{out} in the normal range. (less than 9 mmHg/ml/min).

Of the 47 patients, 33 had opening pressure >25 cmH_2O, and 14 patients had opening pressure between 15 and 24 cmH_2O.

Interestingly, 10 out of the 14 patients with opening pressure less than 25 cmH_2O had raised R_{out} values.

21 patients had high values of both opening pressure and R_{out}.

Only 4 patients had low values of both opening pressure and R_{out}.

43 patients had high values of either opening pressure or R_{out} or both.

Of the 47 patients 12 underwent Lumboperitoneal shunt for diversion of CSF, in view of the visual field defects and improved. Others were on conservative management with Acetazolamide with or without Frusemide.

All patients reported good symptomatic improvement on the day following the lumbar puncture and patients on conservative treatment showed gradual, progressive improvement and none reported back with signs and/or symptoms of worsening.

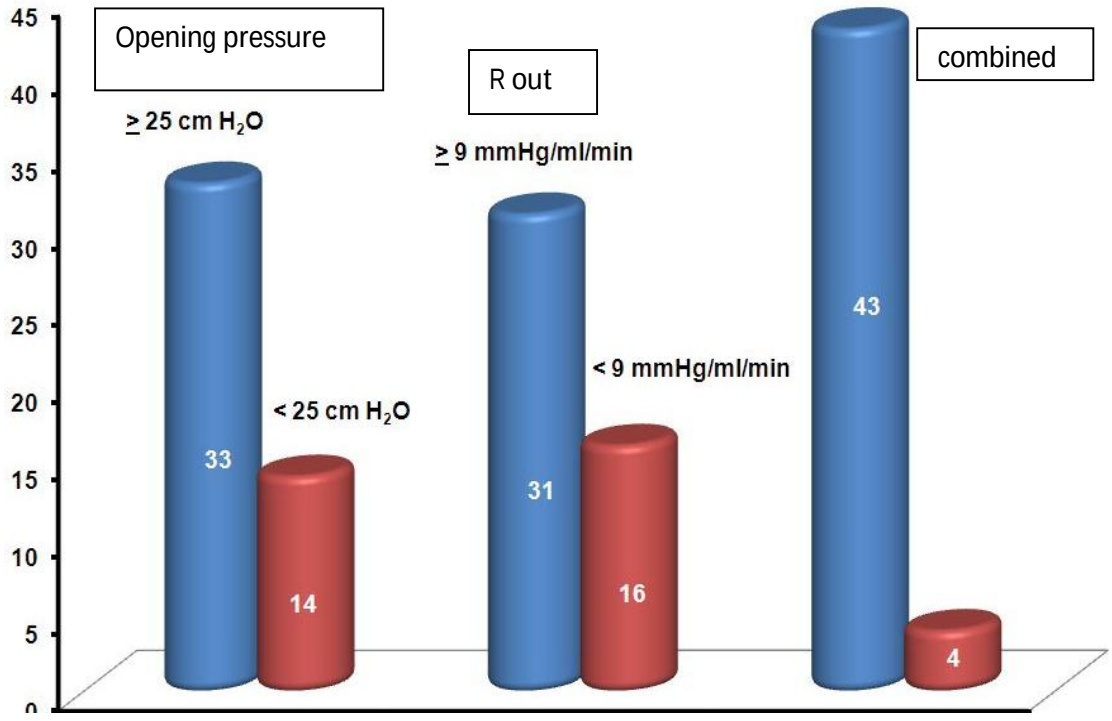

Figure – 7 : Distribution of Opening pressure and R_{out}

Statistical analysis :

Statistical analysis was done using the software SPSS 11.5 and tested the significance of R_{out} measurement, opening pressure measurement, and combined as a criterion for the confirmation of diagnosis of IIH.

Opening Pressure :

One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
TEST1	47	1.70	.462	.067

One-Sample Test

Opening Pressure	Test Value = 0		
	t	Df	Sig. (2-tailed)
	25.243	46	.000

R_{out} :

One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
TEST2	47	1.66	.479	.070

One-Sample Test

R-OUT	Test Value = 0		
	t	df	Sig. (2-tailed)
	23.754	46	.000

Combined opening pressure and R_{out} :

One-Sample Statistics

	N	Mean	Std. Deviation	Std. Error Mean
Combined	47	1.9149	.28206	.04114

One-Sample Test

Combined	Test Value = 0		
	T	df	Sig. (2-tailed)
	46.543	46	.000

The p value was less than 0.05 in all the three cases, implying statistical significance.

It may be noted that :

- 70% of the patients would have their diagnoses confirmed as IIH as per the existing diagnostic criterion of > 25 cmH_2O for opening pressure.
- 66% of the patients would have their diagnoses confirmed as IIH when resistance to outflow of CSF (R_{out}) measurements were made in the CSF dynamics study.
- 71.4% (10 out of 14) of the patients not satisfying the criteria for opening pressure, qualified for a diagnosis of IIH based on R_{out} measurements.
- 91% of the patients (43 of 47) had their diagnosis confirmed as IIH only when both were employed as diagnostic criteria.

DISCUSSION

The important pathophysiological mechanism underlying the development of IIH is an alteration in the CSF dynamics, leading to a reduction in the outflow of CSF. It is postulated that in this condition, there is a relative obstruction to CSF absorption across the arachnoid villi due either to increased resistance within the villi themselves or to an increase in sagittal sinus pressure altering the pressure differential which controls the CSF absorption. Production of CSF continues, possibly at a slightly reduced rate, causing an increase in CSF volume. The increase in intra cranial pressure will restore or increase the gradient across the villi, thus balancing the increase in sinus pressure or the resistance within the villi. The CSF absorption control system is, therefore reset with an increased CSF volume and an increased intra cranial pressure secondary to an impaired absorptive mechanism. With obstruction to CSF flow at the villi, ventricular dilatation will occur only if the increase in CSF volume is too great to be contained within the subarachnoid space.CSF outflow resistance is an objective measure of the degree of CSF absorption defect.

Among the methods available for measurement of R_{out}, the bolus lumbar injection method advocated by Marmarou and evaluated by Marmarou et

al. and Kostelijanetz[58], is a simple bedside test for quick measurement of R_{out} and can be employed in the clinical setting.

The improvised bolus lumbar injection method (the MIN method) further simplifies the procedure using simple bedside equipment.

A comparison between the bolus injection and the other methods has been done in experimental and clinical settings by several studies and most of them found good correlation between the methods, though the bolus method showed slightly lower values of R_{out} compared to other methods.

The other methods, namely constant pressure servo controlled infusion method, constant infusion method, constant infusion and constant pressure method and radio isotope dilution methods are more accurate, but are time consuming, and require expensive and sophisticated equipment and are more suited for experimental and research purposes.

Many investigators have found increased intracranial pressure in the initial phase of IIH[59]. Intracranial Pressure (ICP) may be normal or only moderately increased in the later phase of the disease process[60,61].

Gjerris et al found raised R_{out} in the initial phase in most patients with IIH[60].Calabrese et al found R_{out} to be increased in all patients with IIH[62]. Increased R_{out} was found in 8 of 10 patients by Sklar et al, and half of them were receiving medical treatment.10 out of 12 patients with benign intracranial tension were found to have higher than normal R_{out} values[54].

The opening pressure measurement by lumbar puncture has long been the only tool employed in the diagnosis of IIH, and exists as a diagnostic criterion from the days of Walter Dandy.

Johnston and Paterson in their paper on Benign Intracranial Hypertension have recorded pressure in the lumbar subarachnoid space and simultaneous ventricular CSF pressure and found that the two corresponded extremely closely in all cases, implying the validation of lumbar puncture as representative of ICP.

It has also been noted by them that many patients showed long periods when the pressue remained quite low, or indeed normal, between short periods of marked intracranial hypertension. They also suggest that the diagnosis of Benign Intracranial Hypertension should be based on closely observed clinical and investigative criteria to achieve accuracy of diagnosis[59].

The 14 patients in our study in whom the opening pressure had been below 25cmH_2O, may well represent the above proportion of patients.

The results of our study show encouraging findings in that 71% of the above category showed raised R_{out} values, making R_{out} estimation indispensible in the diagnosis of IIH.

Saadany et al. have suggested the presence of a low pressure variant of IIH, without papilloedema and with borderline CSF pressure of 16 to 20 cmH_2O[63].

They also suggest that although the hallmark of IIH is papilloedema which may be bilateral, assymetrical, or even unilateral yet this condition may present without papilloedema, and that "normal or boderline resting" CSF pressure does not exclude the diagnosis in the presence of suggestive symptoms and signs. It has been observed by Soler et al that due to the wide diurnal fluctuation in CSF pressure, establishing an increased pressure is not always straight forward. For this reason, ‘‘normal’’ levels can be recorded in patients with elevated optic discs[64].

CONCLUSIONS

The conclusions based on our study on 47 patients with Idiopathic Intracranial Hypertension are:

- The Madras Institute of Neurology (MIN) method of improvised lumbar bolus injection method of CSF dynamics is validated as being simple, quick, and able to produce fairly reliable results for R_{out} estimation.

- The estimation of R_{out}, the resistance to outflow of CSF, is valuable and indispensible part of the diagnosis of IIH, especially if the patient has low opening pressure.

- Opening pressure measurement, though useful in many cases of IIH as a confirmatory diagnostic tool, may sometimes give false negative values and hence has to be combined with R_{out} estimations.

- R_{out} estimations, combined with Opening pressure measurement, is a better diagnostic criterion and may be included as an additional criterion for the diagnosis of IIH.

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APPENDICES

Appendix 1: Consent form

நரம்பியல் அறுவைசிகிச்சைத் துறை, சென்னை மருத்துவக்கல்லூரி மற்றும் அரசு பொது மருத்துவமனை, சென்னை - 3.

சுய ஒப்புதல் படிவம் (Consent form)

ஆய்வு செய்யப்படும் தலைப்பு :

"தொலைமறியா மூளைநீர்-அழுத்தத்தில் மூளை-தலைடுவை நீரோட்ட மாற்றங்கள்"

("CSF dynamics study in Idiopathic Intracranial Hypertension")

பங்கு பெறுபவர் பெயர் : வயது : பாலி :

பங்கு பெறுபவர் (✓) குறியிடவும் :

1	மேலே குறிப்பிட்டுள்ள மருத்துவ ஆய்வின் விபரங்கள் எனக்கு விளக்கப்பட்டது. என்னால் கேட்கப்பட்ட அனைத்து சந்தேகங்களுக்கும் தெளிவான விளக்கங்களும் பெறவும் எனக்கு வாய்ப்பு அளிக்கப்பட்டது	
2.	நான் இவ்வாய்வில் தன்னிச்சையாக பங்கேற்கிறேன். எந்த காரணத்தினாலும் எந்த சிகிச்சையும் பாதிப்பும் இன்றி நான் இதிலிருந்து விலகிக்கொள்ளலாம் என்பது எனக்கு விளக்கப்பட்டது.	
3.	இந்த ஆய்வு சம்பந்தமாகவோ, இதை சார்ந்து மேலும் ஆய்வு மேற்கொள்ளவோ, மருத்துவர் என்னுடைய மருத்துவ அறிக்கைகளைப் பார்ப்பதற்கு என் அனுமதி தேவையில்லை என அறிந்துகொள்கிறேன்.	
4.	இந்த ஆய்வின் மூலம் கிடைக்கும் முடிவுகளையோ முடிவுகளையோ பயன்படுத்திக் கொள்ள அனுமதி அளிக்கிறேன்.	
5.	இந்த ஆயிலில் பங்குபெற முழுமனதுடன் சம்மதிக்கிறேன்.	

பங்கேற்பவர் கையொப்பம் விபரம்

சாட்சியாளர் : கையொப்பம் விபரம்

ஆய்வாளர் : கையொப்பம்

நாள் :

இடம் :

Appendix 2 : Ethical Committee Approval

25

INSTITUTIONAL ETHICAL COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI 600 003

Telephone 25363970
Fax 044 2535215
Dated : 12.05.2010

I.Dis.No.14597/MI5/Ethics Dean/MMC/2010

Title of the work : "CSF dynamics study in Idiopathic Intracranial Hypertension."

Principal Investigator : Dr. P. Magesh
Designation : PG in MCh Neurosurgery.
Department :
Madras Medical College & GGH, ch-3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 12th May 2010 at 2.p.m in Pharmacology Seminar Hall, Madras Medical College, Chennai -3

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
4. You should not deviate form the area of the work for which you applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulation of the institution(s).
7. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, MMC, CHENNAI

CHAIRMAN
IEC, MMC, CHENNAI

DEAN
MADRAS MEDICAL COLLEGE,
CHENNAI-3

Appendix 3 : Proforma

CSF Dynamics Study in Idiopathic Intracranial Hypertension

NAME :

AGE:

SEX:

IP No.:

Ward/Unit:

Address:

Date of study:

Brief history:

Clinical findings:

Investigations: CT Brain : MRI +MRV:

Vision chart/ NeuroOphth. Opn.:

CSF Study: P_0 : P_p: Pt: t: rV :

PVI: R_{out}:

Any abnormality in cytology/Biochemistry : Y / N

Management:

Conservative / Surgery

Improvement after LP : Y / N

Follow up:

Remarks:

Appendix - 4 : Master chart.

S. No.	AGE	SEX	OP. PRES	PVI	R out	CONS	SURGERY
1	33	F	31	66.7	11.4	Y	N
2	28	F	21	35.7	9.4	Y	N
3	40	F	18	26.3	6.9	Y	N
4	45	M	37.5	37.6	16.9	Y	N
5	27	F	37	58.8	5.8	N	Y
6	32	F	15	178	2.8	Y	N
7	37	F	19	45.5	22.6	N	Y
8	29	F	42	26.3	53.4	N	Y
9	40	F	40	122	4.3	Y	N
10	36	M	16	16.9	43.7	Y	N
11	21	F	45	53.2	8.1	N	Y
12	28	M	33	132.6	4.7	Y	N
13	26	F	25	33.3	10.3	Y	N
14	36	F	35	42	6.6	N	Y
15	45	M	14	238	27.1	Y	N
16	30	F	25	15.2	27.8	Y	N
17	28	M	49	62.5	15.1	Y	N
18	49	M	21	26.3	10.9	Y	N
19	24	M	65	42	17	N	Y
20	48	F	38	22.7	48.5	N	Y
21	27	F	42.5	15.7	21.4	Y	N
22	30	F	27	50	28.5	Y	N
23	15	F	19.5	40	14.3	Y	N
24	19	F	83	79.3	38	N	Y
25	33	F	41	73.5	4.1	Y	N
26	42	F	47	21.2	61.2	N	Y
27	24	F	39	62.5	5.1	Y	N
28	40	F	60	40	18.3	N	Y
29	23	M	33	36	6.9	Y	N
30	22	F	64	49	25.1	Y	N
31	40	F	55	54.3	10.1	Y	N
32	27	F	25	35.8	7.3	Y	N
33	37	F	24	27.8	13	Y	N
34	40	M	26	20.2	10.9	Y	N
35	30	F	23	43.5	7.8	Y	N
36	32	M	19	43.1	3.2	Y	N
37	41	F	60	39.4	17.9	Y	N
38	29	F	41	58	7.9	Y	N
39	40	M	38	29.8	16.2	Y	N
40	18	F	26	33	8.3	Y	N
41	27	F	35	72	11.5	Y	N
42	24	M	40	53	13.5	N	Y
43	15	F	21	26	9.1	Y	N
44	26	F	35	48	6.2	Y	N
45	42	F	18	74.6	12.2	Y	N
46	22	F	26.5	29.4	14.9	N	Y
47	30	F	18	57.5	8.9	Y	N